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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Bioavailability of Pharmaceutical Active Compounds with Peptide Linkages

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Abstract of the Disclosure: Pharmaceutical active compounds which contain peptide linkages and ar ther fore sensitive are protected from degradation, during passage through the stomach and intestines, by micronization. This improves the absorption and bioavailability. In the micronization the active compounds are extremely finely divided, and each particle is provided with a colloid protective envelope.

Improvement in the bioavailability of pharmaceutical active compounds with peptid linkages

Pharmaceutical active compounds which contain peptide linkages and are therefore sensitive are, according to the invention, protected from degradation, especially during passage through the stomach and intestines, by micronization. This improves the absorption and bioavailability. In the micronization the active compounds are extremely finely divided, and each particle is provided with a colloid protective envelope.

Pharmaceutical active compounds with peptide linkages are usually unstable during passage through the stomach and intestines. This is why relatively large quantities of active compound have to be taken in order to achieve adequate plasma levels. An enteric coating does not solve the problem because the peptide linkages are also rapidly degraded in the intestines. A relatively complex solution is described by M. Saffran and G.S. Kumar in Science 233 (1986) 1081, but this entails undesired slowing of absorption. In addition, the absorption promoters employed therein are not physiologically acceptable.

It is an object of the present invention to develop dry pharmaceutical products containing active compounds with peptide linkages, which are more stable than conventional ones during passage through the stomach and intestines and therefore are absorbed to a greater extent.

We have found that this object is achieved by micronizing the active compound, ie. dissolving it together with a surfactant in a volatile, water-miscible organic solvent at from 5 to 200°C, where appropriate under superatmospheric pressure, within less than 10 seconds, immediately converting the active compound into colloidal form by rapidly mixing the resulting molecular solution with an aqueous solution of a swellable colloid at from 0 to 50°C, and removing the solvent and the

dispersing medium in a conventional manner from the resulting dispersion.

The micronizing process is described for carotenoids and retinoids in EP-A-65 193 for producing colorants for human and animal foods. It was not to be expected that this process could be used to achieve the present object. The active compounds which have been micronized according to the invention are, surprisingly, stable to hydrolysis or enzymatic degradation of the peptide linkages, despite being extremely finely divided. The active compounds are, moreover, absorbed rapidly and to a large extent so that even relatively low doses result in relatively high plasma levels.

Examples of active compounds with peptide linkages are doreptide, polypeptide antibiotics such as tyrothricin and polymyxin B, TNF, immunomodulators such as interferon-γ, renin inhibitors, and ACE inhibitors.

Examples of suitable water-miscible volatile organic solvents are alcohols such as ethanol, n-propanol and iso-propanol, ethers such as 1-methoxy-2-butanol or 1-n-propoxy-2-propanol and ketones such as acetone. They should be at least 10 % water-miscible, boil below 200°C and contain fewer than 10 carbon atoms. Examples of suitable water-soluble or swellable colloids are gelatin, starch, dextrin, dextran, pectin, gum arabic, casein, caseinate, whole milk, skim milk, milk powder, polyvinyl alcohol, polyvinylpyrrolidone, methylcellulose, carboxymethylcellulose, hydroxypropylcellulose, microcrystalline cellulose and alginates. For further details on colloids, reference may be made to R.A. Morton, Fast Soluble Vitamins, Intern. Encyclopedia of Food and Nutrition, Volume 9, Pergamon Press 1970, pages 128-131. In order to increase the mechanical stability of the final product it is possible to add to the colloid a softener, for example a sugar such as sucrose, glucose, lactose or invert sugar, or sugar alcohol such as sorbitol or mannitol, or maltodextrin or glycerol. Minor amounts of, for example,

methylparaben, propylparaben, sorbic acid and/or sodium benzoate can be added as preservatives.

Examples of suitable surfactants (dispersants) are esters of long-chain fatty acids with citric acid, lactic acid, tartaric acid or ascorbic acid, especially ascorbyl palmitate, mono- and diglycerides of fatty acids and the ethoxylation products thereof, polyglycerol fatty acid esters (eg. the monostearate of triglycerol), sorbitan fatty acid esters, propylene glycol fatty acid esters, salts of 2-(2-stearoyllactyl)lactic acid and lecithin. Depending on the solubility, the surfactant is dissolved either in the organic solvent (together with the active compound) or in the aqueous phase.

Further pharmaceutical auxiliaries such as binders, disintegrants, flavorings, vitamins, colorants, wetting agents and additives to alter the pH (cf. H. Sucker et al., Pharmazeutische Technologie, Thieme-Verlag, Stuttgart 1978) can also be introduced in the solvent or the aqueous phase. It is self-evident that all pharmaceutical auxiliaries must be physiologically acceptable.

The ratio of colloid and softener to solution of active compound and surfactant is generally selected to result in a final product which contains from 0.5 to 40, preferably about 20, % by weight of active compound, from 0.1 to 30, preferably 5 to 15, % by weight of one or more surfactants, from 10 to 50 % by weight of a swellable colloid, from 0 to 70 % by weight of a softener, all percentages being based on the dry mass of the powder, and, where appropriate, minor amounts of a stabilizer, with the powder having a mean particle size of the active compound less than 0.8 μm and a half-width of the particle size distribution of less than 50 %, and virtually no particles are over 1 μm in size.

Examples of suitable stabilizers are α-tocopherol, butylated hydroxytoluene, butylated hydroxyanisole and ethoxyquine. Like the surfactant, they can be added

either to the aqueous or to the solvent phase, d pending on solubility.

The process according to the invention is carried out, for example, in an apparatus like that depicted in Fig. 1, specifically as follows:

The apparatus comprises parts I, II and III. Part II is the high-temperature zone if required. Parts I and III are generally at below 50°C.

A suspension of the active compound in the solvent and possibly one or more surfactants, with or without a small amount of added stabilizers, is placed in vessel (1). Particularly rapid dissolution of active compounds which are sensitive to heat or sparingly soluble at room temperature can be achieved by previous milling (particle size <50 μm). Vessel (2) contains a solvent without active compound. Pumps (3) and (4) deliver the suspension of active compound and the solvent to the mixing chamber, it being possible to choose the mixing ratio by the choice of the delivery rates of each of the pumps so that, depending on the solubility of the active compound in the solvent and the desired residence time, the concentration of active compound in the mixing chamber is from 0.5 to 10 % by weight based on the solution. In the case of thermolabile active compounds, the volume of the mixing chamber (7) is preferably such that the residence time in (7) is less than 1 second at the set delivery rates of pumps (3) and (4). Before the solvent enters the mixing chamber it is brought to the desired temperature in the heat exchanger (6), while the suspension of active compound is maintained at below 50°C during transfer through the line (5) (which is thermally insulated when the active compound is sensitive to heat). Turbulent mixing in (7) at from 10 to 240°C, preferably from 100 to 200°C (for active compounds which are only slightly soluble even in the best solvent at room temperature), causes the active compound and the stabilizer to dissolve, and the resulting solution passes via the

overflow (8) into the second mixing chamber (11) where, by mixing in an aqueous protective colloid/soften r solution, which also contains the surfactant if this has not been dissolved in the organic solvent, via the pump (9) and the line (10), a microdispersion of the active compound (micronizate) is formed from the molecular solution of active compound and the aqueous phase. The dispersion is then discharged via the line (12) and the pressure control valve (13) and collected in the storage vessel (14). It is possible, in order to maximize the concentration of active compound, to circulate the dispersion via the suction line (15).

When the pressure control valve (13) is set at pressures above 1 bar, it is even possible in the novel process to use solvents at temperatures above their boiling point (under atmospheric pressure).

It is possible to obtain from the dispersion a product in the form of a powder in a conventional manner, eg. as described in DE-A 25 34 091, for example, by spray granulation, spray drying or spray cooling and coating of the particles, removal and drying in a fluidized bed.

For the spray drying, either the solvent is first removed from the dispersion by distillation, preferably under reduced pressure, or by extraction with a water-immiscible solvent, or the entire mixture is spray-dried and thus water and solvent are removed together in the spray tower.

The active compound powder discharged from the spray tower is usually dry and free-flowing. It may be expedient in some cases to complete the drying by additional treatment in a fluidized bed.

The production of the powder by spray drying can be replaced by any other suitable methods for converting the active compounds, which are already finely divided in the water/active compound dispersion, into the form of a powder. A conventional process, which can be used when the auxiliaries and protective colloids can be converted

into g ls comprises, for exampl , removing the solv nt from the dispersion and producing a W/O emulsion in liquid paraffin, converting the emulsion droplets into a gel by cooling, removing the paraffin from the particles, and washing the resulting material with petroleum spirit and drying in a fluidized bed. It is also possible to concentrate the dispersion of active compound by coacervation followed by filtration.

In each case, the result is a dry powder which can be dissolved or redispersed in water to achieve a uniform distribution of the active compound in the particle size range below 1 μm.

The powders which can be obtained according to the invention can be converted in a conventional manner into the following pharmaceutical forms: uncoated or (film-)coated tablets, capsules or instant powders. They can also be used as intermediates for producing lyophilizates and solutions for injection.

Determination of the bioavailability in dogs:

The micronized substance (doreptide) is administered to dogs by gavage (dose 50 mg/kg), and blood is taken from the animals at defined times. After the plasma has been obtained, the samples are immediately deep-frozen and analyzed later by means of HPLC (reverse phase, fluorescence detection after derivatization). The plasma levels found in this way are compared with those found in the same dogs (after a 1-week washout period) after administration of the same dose of doreptide tablets produced in a conventional manner.

EXAMPLE 1

12 g of L-prolyl-2-phenyl-L-2-aminobutanoyl-glycinamide (doreptide) were suspended in a vigorously stirred mixture of 2.4 g of ascorbyl palmitate and 40 g of isopropanol and, with the pressure control valve (13) set at 25 bar, mixed in the mixing chamber (7) with isopropanol which had been heated to 200°C in the heat exchanger (6). With a delivery rate for the suspension of

0.26 l/h and for the solvent of 0.38 l/h, the resid nce time in the mixing chamb r (7) was 0.6 seconds. The resulting molecular solution was then transferred into the mixing chamber (11) where a doreptide dispersion was produced by turbulent mixing with a solution of 15 g of gelatin and 22.5 g of sucrose per liter, which had been adjusted to pH 11 with 1N NaOH. The temperature of the dispersion in the collecting vessel (14) was 30°C. Particle size analysis by photon correlation spectroscopy (B. Chu, Laser Light Scattering Analysis, Academic Press, New York 1974) showed that the mean particle diameter was 370 nm with a distribution range of ± 60 %.

Spray drying resulted in an easily handled, water-soluble dry powder which contained 16.5 % doreptide. Resuspension of the dry powder in cold water yielded a dispersion with a mean particle size of 300 nm ± 55 %.

EXAMPLE 2

10 g of gramicidin S were suspended in a mixture of 1.2 g of ascorbyl palmitate and 40 g of isopropanol and micronized in the same way as in Example 1. The particle size distribution of the micronizate corresponded to that from Example 1.

EXAMPLE 3

11 g of N-[(1-ethyl-2-pyrrolidinyl)methyl]-2-methoxy-5-sulfamoylbenzamide (sulpiride) were suspended in a mixture of 2.0 g of ascorbyl palmitate and 40 g of methanol and micronized in the same way as in Example 1. The mean particle size of the micronizate was 390 nm ± 40 %.

EXAMPLES 4 TO 11

The active compounds listed in the following Table 1 can be converted into micronizates in the same way as described in Example 1, the physicochemical properties of the micronizates being in agreement with those in Example 1.

TABLE 1

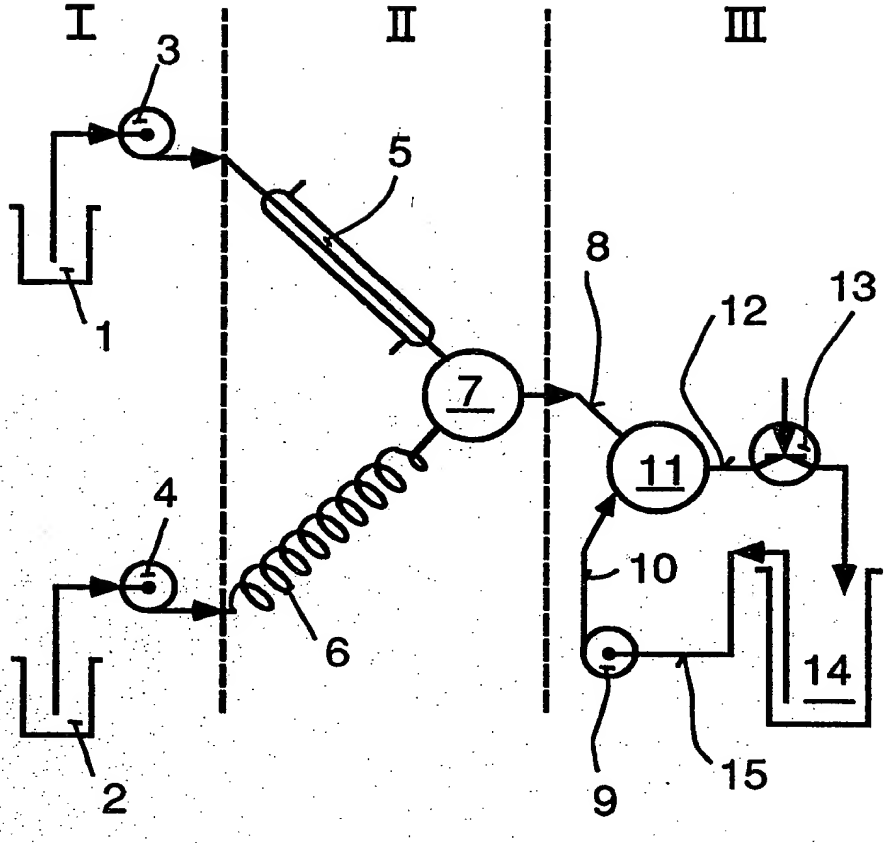
Example	Active compound
4	Tyrothricin; Merck Index 9640 (10th edition)
5	Polymyxin B from Fluka, D 7910 Neu-Ulm
6	1-(3-Mercapto-2-methyl-1-oxopropyl)-L-proline (captopril)
7	1-[N-[(S)-1-Carboxy-3-phenylpropyl]-L-alanyl]-L-proline-1'-ethyl ester maleate (enalapril maleate)
8	2(S)-[N-(Morpholinocarbonyl)-L-phenylalanyl-N^{α}-methyl-L-histidylamino]-1-cyclohexyl-3(S)-hydroxy-6-methylheptane
9	N-Butyl-6-cyclohexyl-4-hydroxy-2-isopropyl-5-[N-[2-(3,3-dimethyl-2-oxobutyl)-3-phenylpropanoyl]-L-histidylamino]-hexanamide
10	[N-(3-Amino-3-methyl-1-oxobutyl)-4-methoxy-L-phenylalanyl]-N-[(1S,2R,3S)-1-(cyclohexylmethyl)-2,3-dihydroxy-5-methylhexyl]-L-histidineamide
11	2-Acetamido-3-O-[(R)-1-[[(S)-1-[[(R)-3-carbamoyl-1-carboxypropyl]carbamoyl]ethyl]carbamoyl]ethyl]-2-deoxy-D-glucopyranose butyl ester (murabutide)

We claim:

1. A process for improving the bioavailability of pharmaceutical active compounds with peptide linkages, which comprises dissolving the particular active compound with or without a surfactant in a volatile, water-miscible organic solvent at from 5 to 200°C, where appropriate under superatmospheric pressure, within less than 10 seconds, immediately precipitating the active compound in the form of a colloid from the resulting molecular solution by rapid mixing with an aqueous solution or dispersion of a solid or swellable colloid (and of a surfactant if this had not already been dissolved in the organic phase) at from 0 to 50°C, and converting the resulting dispersion into a redispersible powder by removing the solvent and the dispersing medium from it in a conventional manner.

2. A process as claimed in claim 1, wherein the components are employed in amounts such that the resulting powder has the following composition:

0.5 to 40 % by weight active compound
0.1 to 30 % by weight surfactant
10 to 50 % by weight swellable colloid
0 to 70 % by weight softener
0 to 70 % by weight one or more conventional pharmaceutical auxiliaries



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